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Phase 1/2 Study of the Activin Receptor-Like Kinase-2 (ALK2) Inhibitor Zilurgisertib (INCB000928, LIMBER-104) as Monotherapy or With Ruxolitinib in Patients With Anemia Due to Myelofibrosis

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Introduction

- Elevated levels of the iron regulator hepcidin can cause functional iron deficiency anemia[1]
  - Hepcidin dysregulation is central to anemia of chronic inflammation observed in several malignancies such as myelofibrosis (MF)[2]
  - MF-related anemia is associated with poor prognosis[3,4] and reductions in health-related quality of life[5]
- ALK2 (also known as ACVR1) contributes to MF-associated anemia via hepcidin upregulation[4,6]

Objective

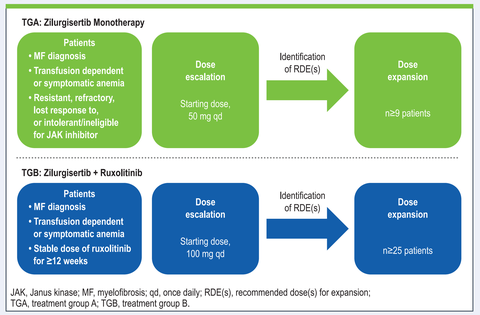
- Evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics of zilurgisertib, a potent and selective, oral ALK2 inhibitor, in patients with anemia due to MF

Methods

Study Design and Patients

- This ongoing open-label, multicenter, phase 1/2 dose-escalation/expansion study (INCB 00928-104; NCT04455841) is evaluating zilurgisertib alone (treatment group A [TGA]) or with ruxolitinib (treatment group B [TGB]; **Figure 1**)

Figure 1. Study Design



JAK, Janus kinase; MF, myelofibrosis; qd, once daily; RDE(s), recommended dose(s) for expansion; TGA, treatment group A; TGB, treatment group B.

- Eligible patients were ≥18 years old with histologically confirmed primary or post-polycythemia vera (PV)/essential thrombocythemia (ET) MF of intermediate (Int)-1 (TGB only) or Int-2/high-risk (TGA and TGB) per the Dynamic International Prognostic Scoring System (DIPSS)
  - Patients were transfusion dependent (≥4 units of red blood cell transfusions during the 28 days or 8 weeks before Cycle [C] 1 Day [D] 1 for hemoglobin [Hb] <8.5 g/dL in the absence of bleeding or treatment-induced anemia) or presented with symptomatic anemia (Hb <10 g/dL during screening on 3 separate occasions ≥7 days apart)
  - In TGA, patients were resistant, refractory, or had lost response to Janus kinase (JAK) inhibitor treatment (≥12 weeks) or were intolerant of or not eligible for JAK inhibitor treatment
  - In TGB, patients were on a therapeutic and stable regimen of ruxolitinib for ≥12 weeks
- The TGA zilurgisertib starting dose was 50 mg once daily (qd), with dose increases of ≤2-fold performed until a grade ≥2 toxicity with reasonable probability of being related to the treatment group was observed; subsequent dose increases were limited to ≤50% until the maximum tolerated dose (MTD) was reached or the recommended dose(s) for expansion (RDE[s]) were identified
- The TGB starting dose was 100 mg qd (half of the safe and tolerated dose, as determined in a study in healthy volunteers)

Study Endpoints

- The primary endpoint is safety and tolerability of zilurgisertib ± ruxolitinib, including determination of dose-limiting toxicities (DLTs), MTD, and RDE(s)
- Secondary endpoints include efficacy (per anemia response parameters), PK, and pharmacodynamics (eg, hepcidin [reported here]; erythropoiesis and iron metabolism parameters [to be reported separately])
  - Anemia response if not transfusion-dependent at baseline: Hb increase ≥1.5 g/dL for any rolling 12-week period during first 24 weeks of treatment
  - Anemia response if transfusion-dependent at baseline: achieving transfusion independence for any rolling 12-week period during first 24 weeks of treatment

Pharmacokinetics

- Blood sampling for PK analyses was performed at C1D1 and C1D15 (predose and 2, 4, and 6–8 hours postdose)
- Target thresholds include protein binding–adjusted 50% or 90% inhibitory concentration (IC_{50}/IC_{90}) values for inhibition of bone morphogenic protein (BMP)-7–induced hepcidin in human primary hepatocytes and IC_{50} value for inhibition of pSMAD1 observed in an in vivo mouse model (target value shown is adjusted to correspond to human protein binding)

Pharmacodynamics: Hepcidin Measurement

- Hepcidin concentration was measured from plasma on C1D1 and C1D15 (predose and at 2, 4, and 6–8 hours postdose; predose only shown for C1D15) and on D1 of subsequent cycles (predose measurement only)
- Plasma hepcidin was measured using a validated fluorometric immunoassay (ProteinSimple hepcidin assay, Ella automated system; Biotechne, Minneapolis, MN)

Results

Baseline Characteristics

- A total of 36 patients were enrolled at the time of analysis (data cutoff date, February 15, 2023), including 20 in TGA and 16 in TGB (**Table 1**)
- Median ruxolitinib starting daily dose was 10 mg bid (20.0 mg daily; range, 15–50 mg)

Safety

- At the time of analysis, dose escalation was ongoing in both treatment groups
- No DLTs occurred in either treatment group
- MTD had not been reached at the time of analysis

Table 1. Demographics and Clinical Characteristics at Baseline

	TGA (n=20)	TGB (n=16)
Age, median (range), y	73.0 (53–84)	75.5 (54–85)
Men, n (%)	13 (65.0)	7 (43.8)
Race, n (%)		
White	14 (70.0)	11 (68.8)
Black	2 (10.0)	0
Asian	3 (15.0)	2 (12.5)
Other	1 (5.0)	3 (18.8)
Time since first MF diagnosis, median (range), y	2.4 (0.2–23.1)	7.2 (1.4–24.1)
DIPSS risk level, n (%)		
High	1 (5.0)	3 (18.8)
Intermediate-2	19 (95.0)	13 (81.3)
Prior MF therapy, n (%)		
Ruxolitinib	13 (65.0)	16 (100)
Other JAKi	3 (15.0)	2 (12.5)
Other	9 (45.0)	8 (50.0)
Transfusion dependent,* n (%)	11 (55.0)	4 (25.0)
Hb, median (range),† g/dL	7.7 (6.5–9.7)	8.0 (5.1–9.0)
Hepcidin, median (range),‡ ng/mL	171 (18–535)	126 (7–421)

C1D1, Cycle 1 Day1; DIPSS, Dynamic International Prognostic Scoring System; Hb, hemoglobin; JAKi, Janus kinase inhibitor; MF, myelofibrosis; qd, once daily; RBC, red blood cell; TGA, treatment group A; TGB, treatment group B.
* Defined as patients who have received ≥4 units of RBC transfusions during the 28 days before C1D1, or have received ≥4 units of RBC in the 8 weeks before C1D1 for an Hb level of <8.5 g/dL in the absence of bleeding or treatment-induced anemia; the most recent transfusion must have occurred within 28 days before C1D1.
† Baseline Hb was determined as the average of values obtained during the 3 months prior to C1D1 which met the following criteria: Hb value was obtained outside the 14-day washout period following a RBC transfusion or Hb value triggered a RBC transfusion (even if obtained within the 14-day period following a transfusion).
‡ Normal range, 0–50 ng/mL.

- Treatment-emergent AEs (TEAEs) were mainly low grade (**Table 2**) without apparent dose dependency
- Grade ≥3 TEAEs occurred in 11 pts, with thrombocytopenia the most common (n=4; **Table 2**)
- A treatment-related TEAE led to study drug discontinuation in 1 patient (grade 2 hyperferritinemia; 200 mg TGB)

Table 2. Treatment-Emergent Adverse Events Occurring in ≥3 Patients in Either Group

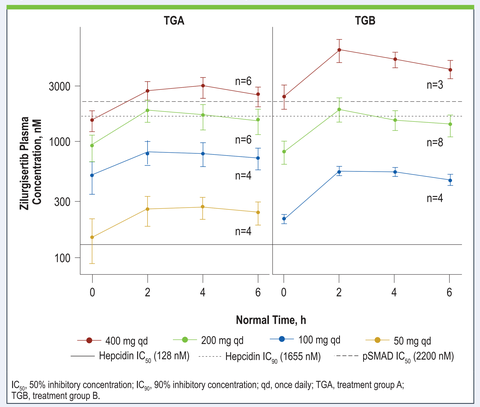
	TGA (n=20)		TGB (n=16)	
Event, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperuricemia	5 (25.0)	0	1 (6.3)	0
Nausea	5 (25.0)	0	2 (12.5)	0
Dyspnea	4 (20.0)	0	3 (18.8)	0
Edema peripheral	4 (20.0)	0	1 (6.3)	0
COVID-19	3 (15.0)	2 (10.0)	1 (6.3)	0
Cough	3 (15.0)	0	1 (6.3)	0
Dysphagia	3 (15.0)	0	1 (6.3)	0
Epistaxis	3 (15.0)	0	1 (6.3)	1 (6.3)
Fatigue	3 (15.0)	0	0	0
Insomnia	3 (15.0)	0	0	0
Myalgia	3 (15.0)	0	0	0
Pruritus	3 (15.0)	0	1 (6.3)	0
Thrombocytopenia	3 (15.0)	3 (15.0)	3 (18.8)	1 (6.3)
Vomiting	3 (15.0)	0	1 (6.3)	0
Asthenia	2 (10.0)	0	3 (18.8)	1 (6.3)
Hyperkalemia	2 (10.0)	0	4 (25.0)	0
Urinary tract infection	1 (5.0)	0	3 (18.8)	0

qd, once daily; RUX, ruxolitinib; TGA, treatment group A; TGB, treatment group B.

Pharmacokinetic Profile

- The PK profile for zilurgisertib at steady state is shown in **Figure 2**
  - t_{max} was attained at 2–4 hours following zilurgisertib administration across dose groups
  - The PK profile predicts a $t_{1/2}$ consistent with that determined in previous healthy volunteer studies (mean, 24–27 h across dose groups)
  - A dose of zilurgisertib 400 mg qd provides exposure at trough above the target thresholds for pSMAD1 and hepcidin inhibition

Figure 2. Zilurgisertib PK Profile at Steady State

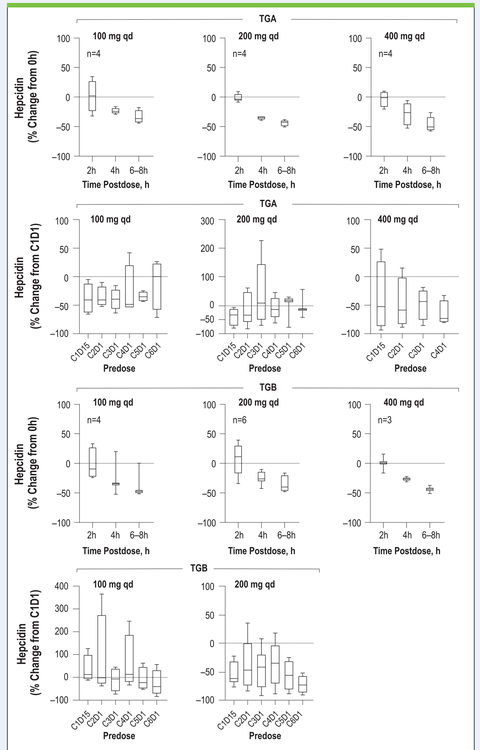


IC_{50}, 50% inhibitory concentration; IC_{90}, 90% inhibitory concentration; qd, once daily; TGA, treatment group A; TGB, treatment group B.

Pharmacodynamic Activity

- Maximum reduction in hepcidin following zilurgisertib dosing on C1D1 was observed at 6–8 h postdose (**Figure 3**)
- Zilurgisertib doses of 400 mg qd in TGA and 200 mg qd in TGB demonstrated greater control of hepcidin suppression over time compared with lower doses in either cohort

Figure 3. Hepcidin Daily Change Following Zilurgisertib Dosing*

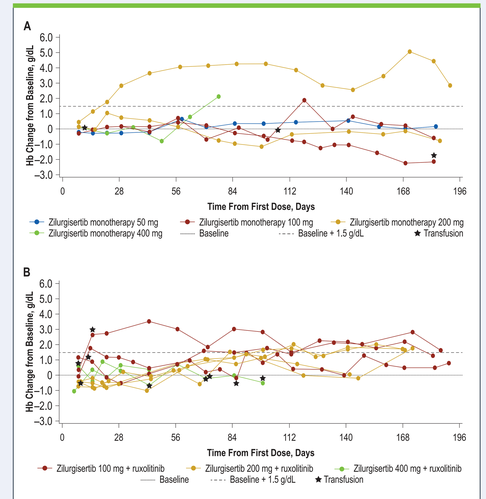


C, Cycle; D, Day; qd, once daily; TGA, treatment group A; TGB, treatment group B.
Top row of TGA and TGB: hepcidin changes following first zilurgisertib dose on C1D1; bottom row of TGA and TGB: morning hepcidin levels (prior to zilurgisertib dose) on Day 1 of each cycle.
* Data shown for patients who completed ≥1 treatment cycle. Hepcidin data beyond Cycle 1 for patients in the TGB 400 mg qd cohort were limited at time of data cutoff, and will be reported separately.

Anemia Responses

- Among nontransfusion–dependent patients, anemia improvement (defined as Hb increase of ≥1.5 g/dL relative to baseline) was observed in 1 of 6 patients in the TGA cohort (200 mg qd dose) and 3 of 9 patients in the TGB cohort (100 mg and 200 mg qd doses; **Figure 4**)
- Of the patients with anemia improvement, 2 achieved anemia response duration of >12 weeks at the time of data cutoff
- All patients with anemia response have maintained a Hb improvement in the absence of transfusion and remain on study
- Among transfusion–dependent patients, anemia response was only evaluable in the TGA cohort at the time of data cutoff; none of the 11 evaluable patients achieved anemia response

Figure 4. Hemoglobin Changes Over Time in Patients in TGA (A) or TGB (B) Who Were Nontransfusion–Dependent at Baseline*



TGA, treatment group A; TGB, treatment group B.
* Data shown for patients who completed ≥3 treatment cycles.

Conclusions and Future Directions

- **Treatment with zilurgisertib monotherapy or in combination with ruxolitinib in this patient population was generally well tolerated, with predominantly grade 1/2 TEAEs and no DLTs**
- **Reduced hepcidin levels were observed at all dose levels with both monotherapy and in combination with ruxolitinib, with greater control of hepcidin over time observed at higher doses**
- **Preliminary improvements in anemia were observed in nontransfusion-dependent patients, which suggest potential for therapeutic activity**
- **Enrollment of transfusion-dependent patients in the combination cohort is ongoing and results will be reported separately**
- **Enrollment of an additional cohort is planned, which will evaluate zilurgisertib plus ruxolitinib as first-line treatment in JAK inhibitor naive patients with MF and anemia**

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